**CHIMERIC PROTEINS AND METHODS OF IMMUNOTHERAPY**

## ABSTRACT OF THE DISCLOSURE

The present disclosure provides systems for immune cell regulation and methods of immunotherapy. Systems of the present disclosure for immune cell regulation comprise a chimeric receptor polypeptide, a chimeric adaptor polypeptide, a gene modulating polypeptide (GMP), and a cleavage moiety.

[Figure 1]

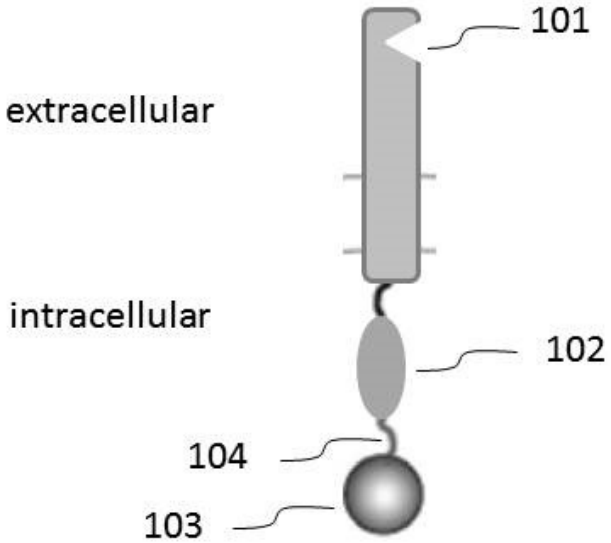



*FIGURE 1*

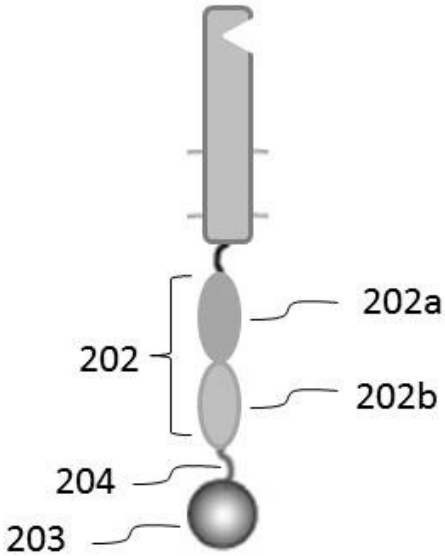



*FIGURE 2*

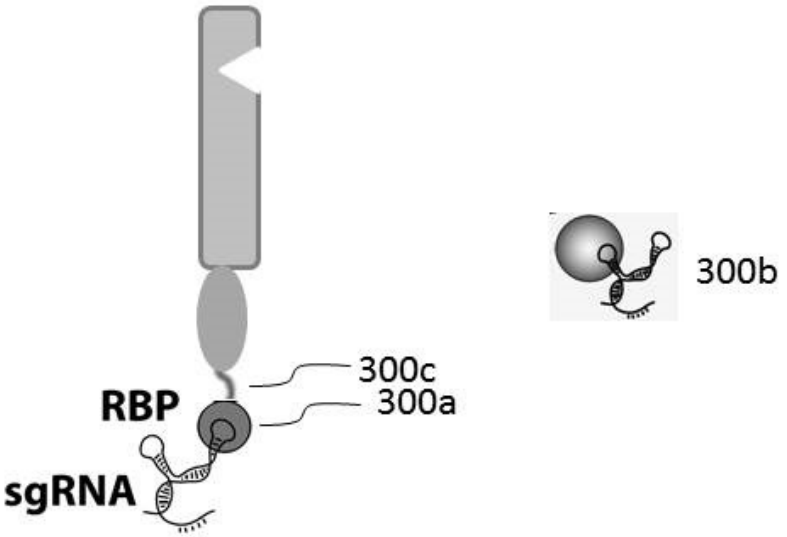



*FIGURE 3A*

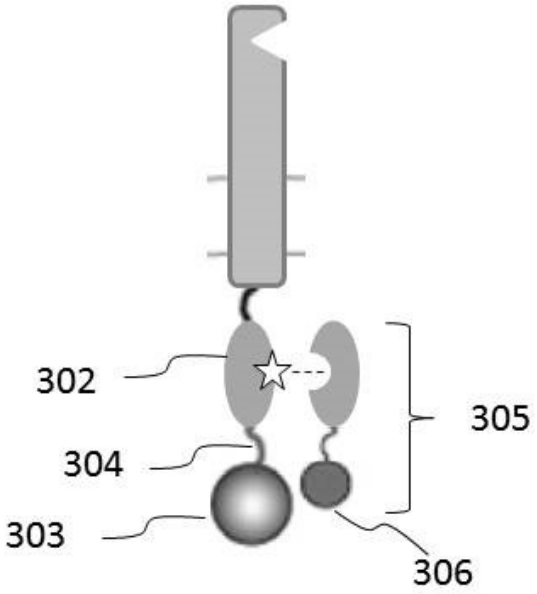



*FIGURE 3B*

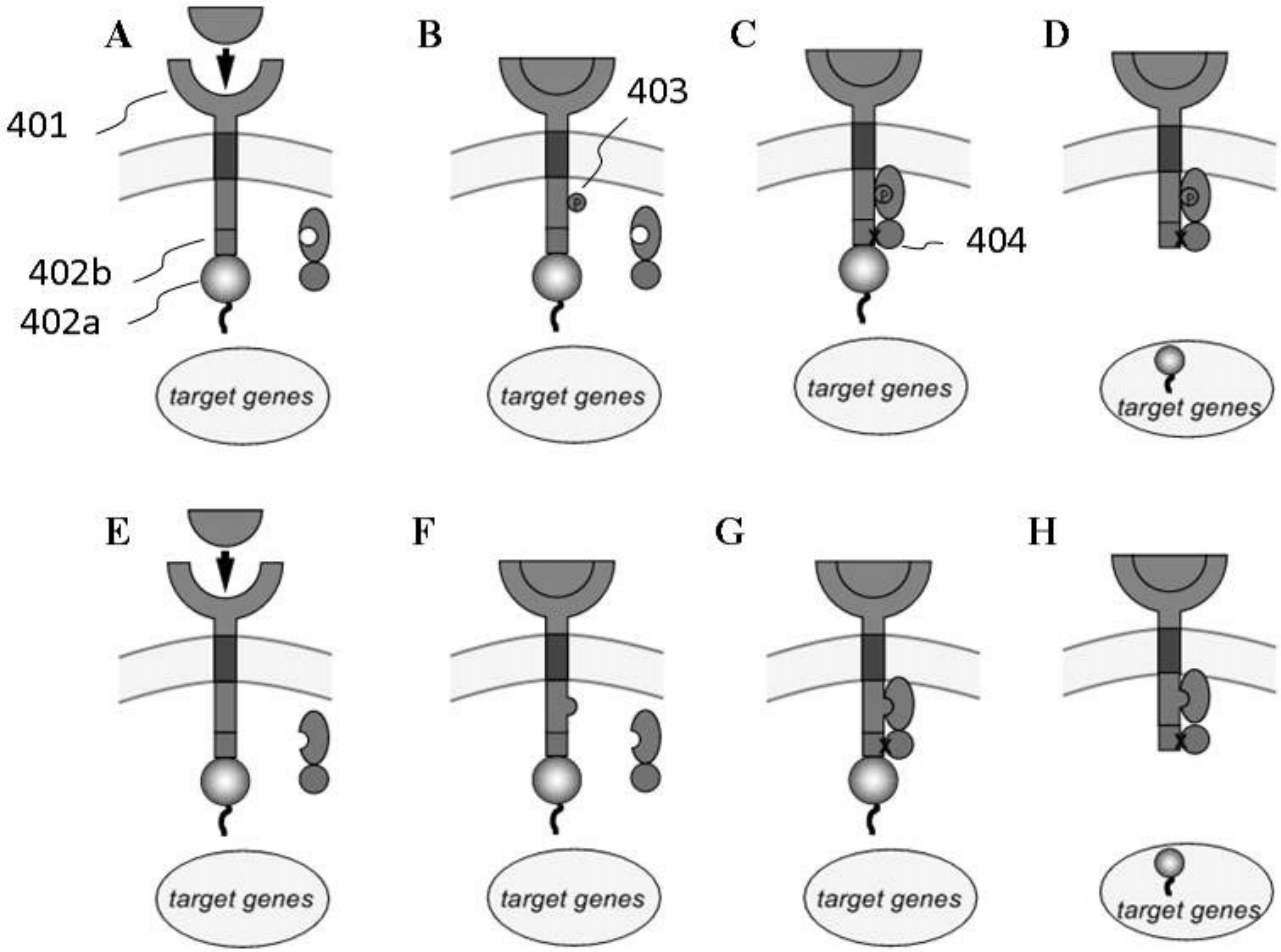

A
B
C
D
401
403
404
402b
402a
target genes
target genes
target genes
target genes
E
F
G
H
target genes
target genes
target genes
target genes

*FIGURE 4*

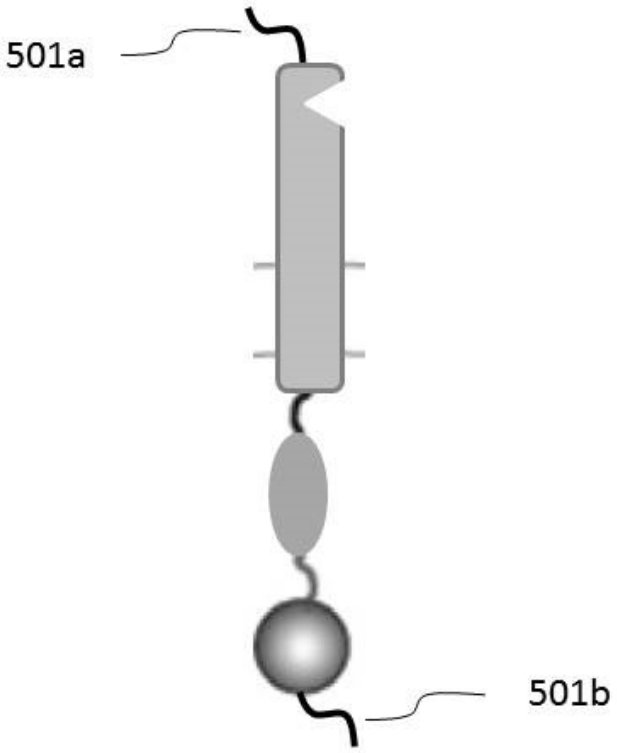



***FIGURE 5***

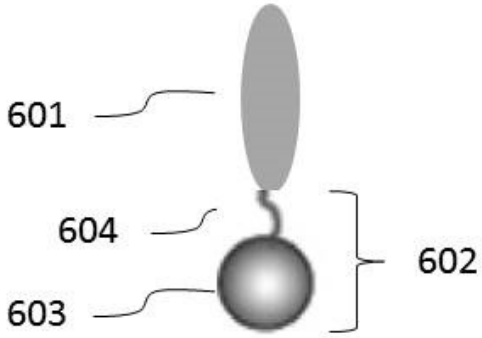



*FIGURE 6A*

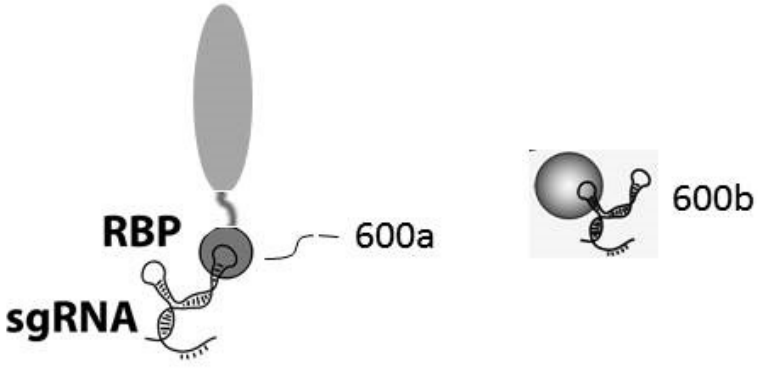



*FIGURE 6B*

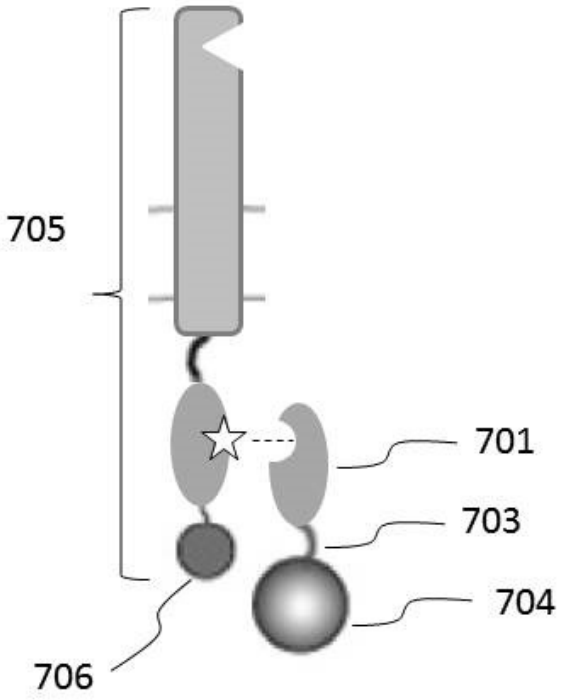



***FIGURE 7***

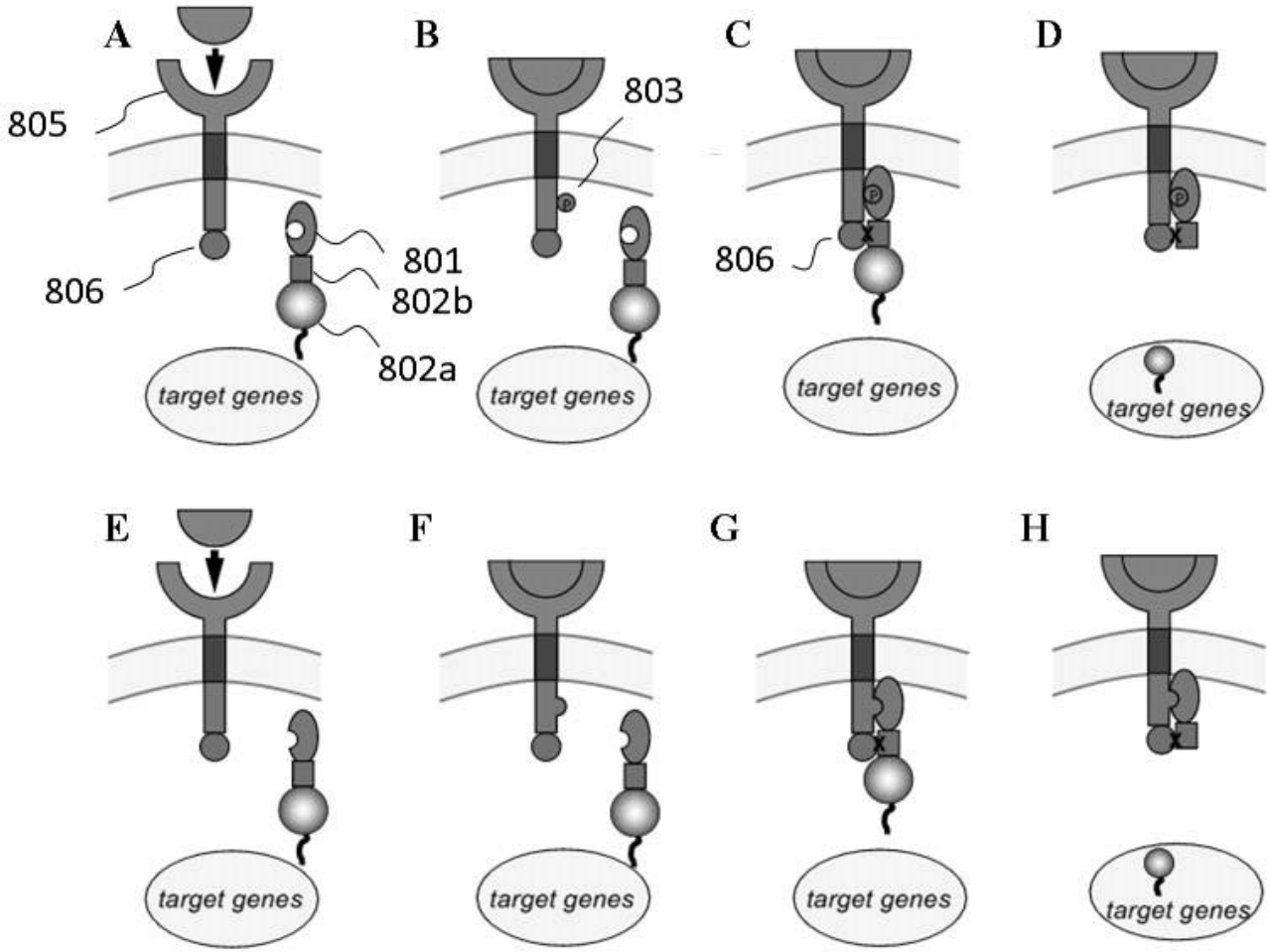

A
B
C
D
805
803
806
801
802b
802a
target genes
target genes
target genes
target genes
E
F
G
H
target genes
target genes
target genes
target genes

*FIGURE 8*

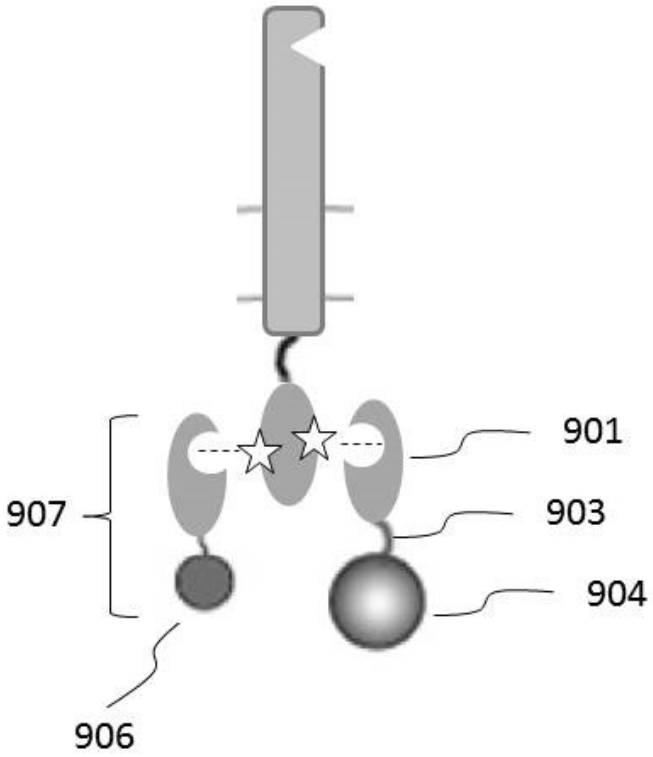



***FIGURE 9***

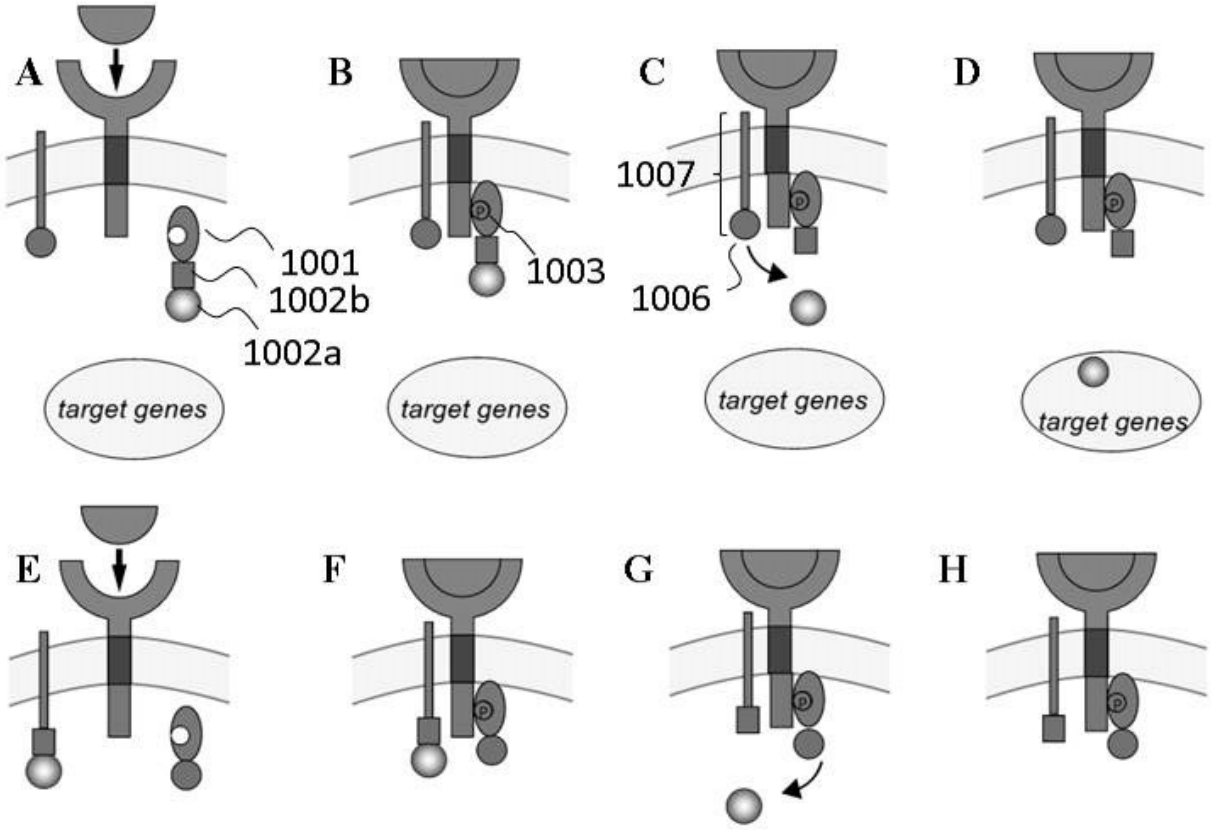

A
B
C
D
1001
1002b
1002a
1003
1007
1006
target genes
target genes
target genes
target genes
E
F
G
H

*FIGURE 10*

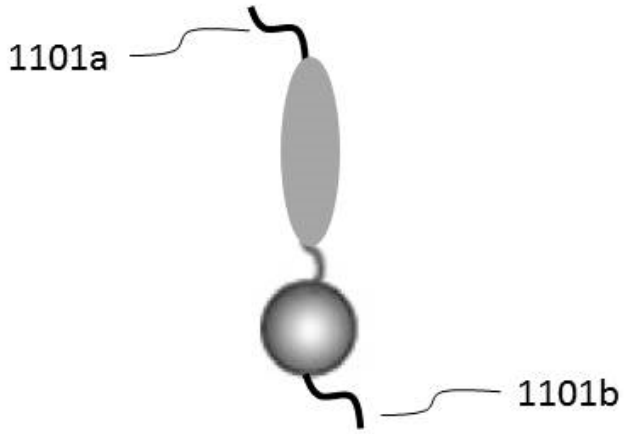



***FIGURE 11***

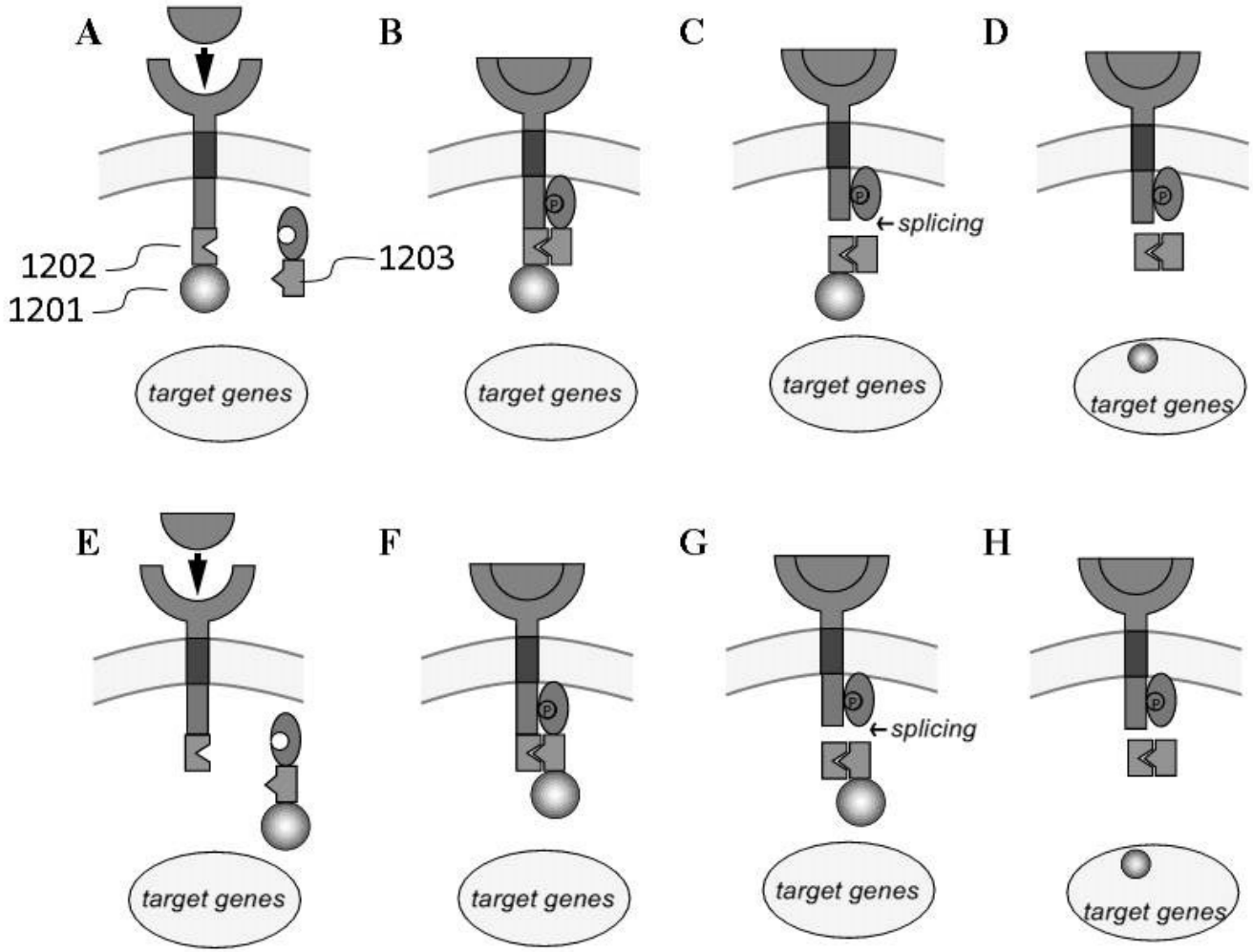

A
B
C
D
1202
1201
1203
splicing
target genes
target genes
target genes
target genes
E
F
G
H
target genes
target genes
splicing
target genes
target genes

*FIGURE 12*

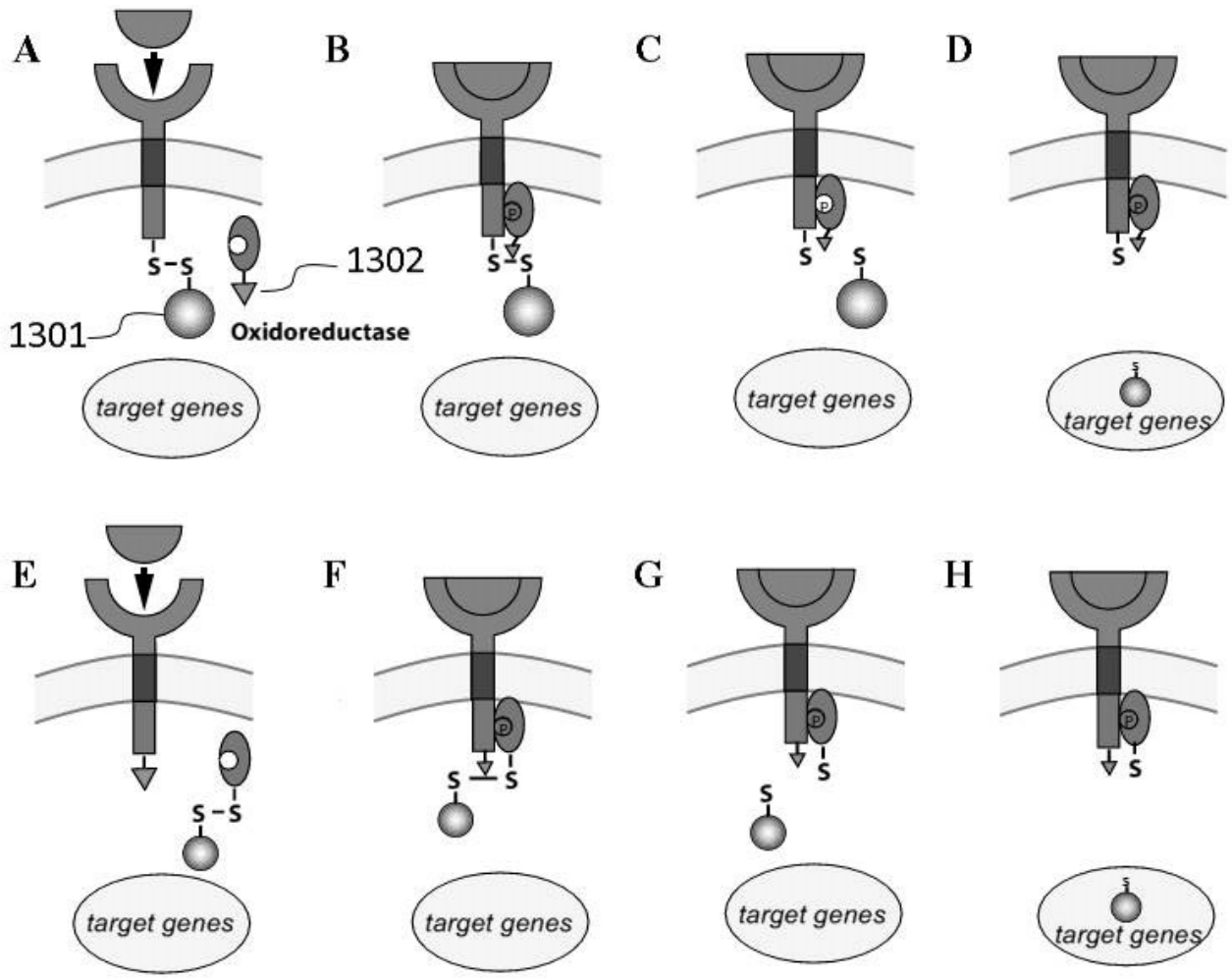

A
B
C
D
1302
1301
Oxidoreductase
target genes
target genes
target genes
target genes
E
F
G
H
target genes
target genes
target genes
target genes

*FIGURE 13*

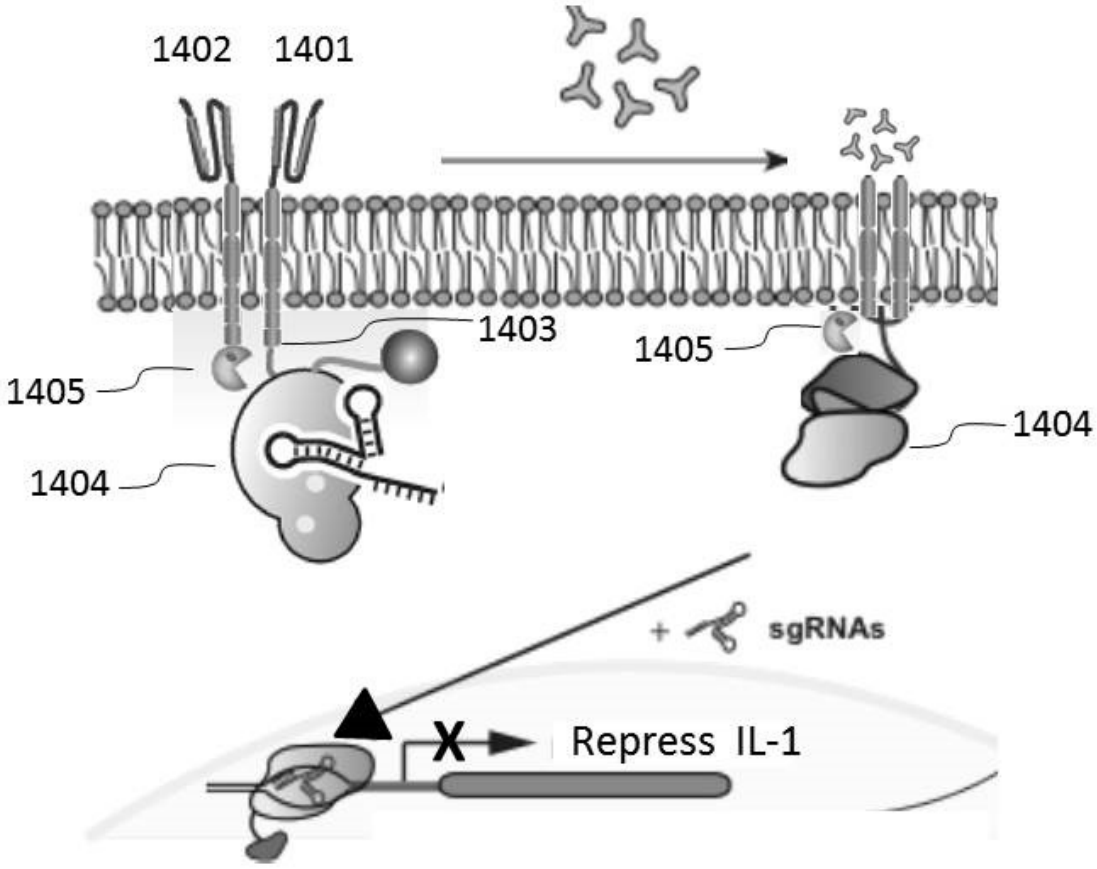

1402
1401
1403
1405
1404
1405
1404
+ sgRNAs
X
Repress IL-1
Nucleus

***FIGURE 14***

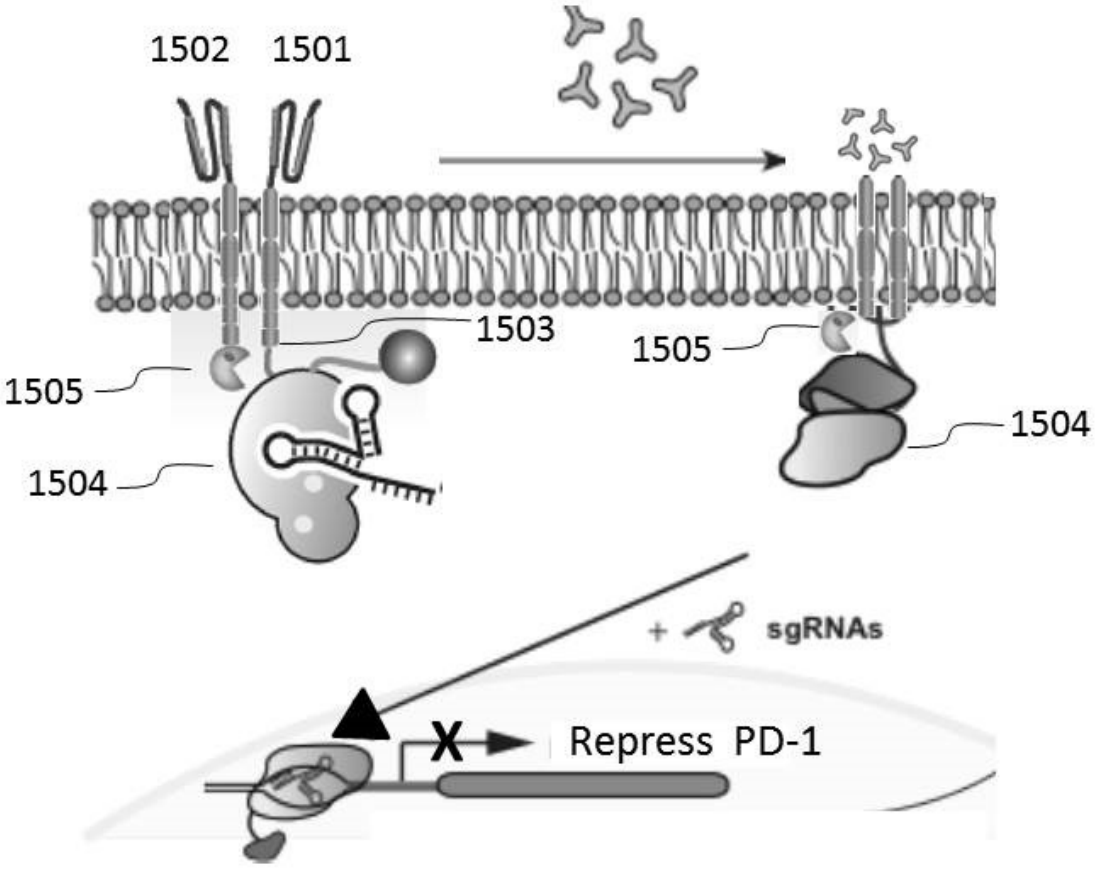

1502
1501
1503
1505
1504
1505
1504
+ sgRNAs
X
Repress PD-1
Nucleus

***FIGURE 15***

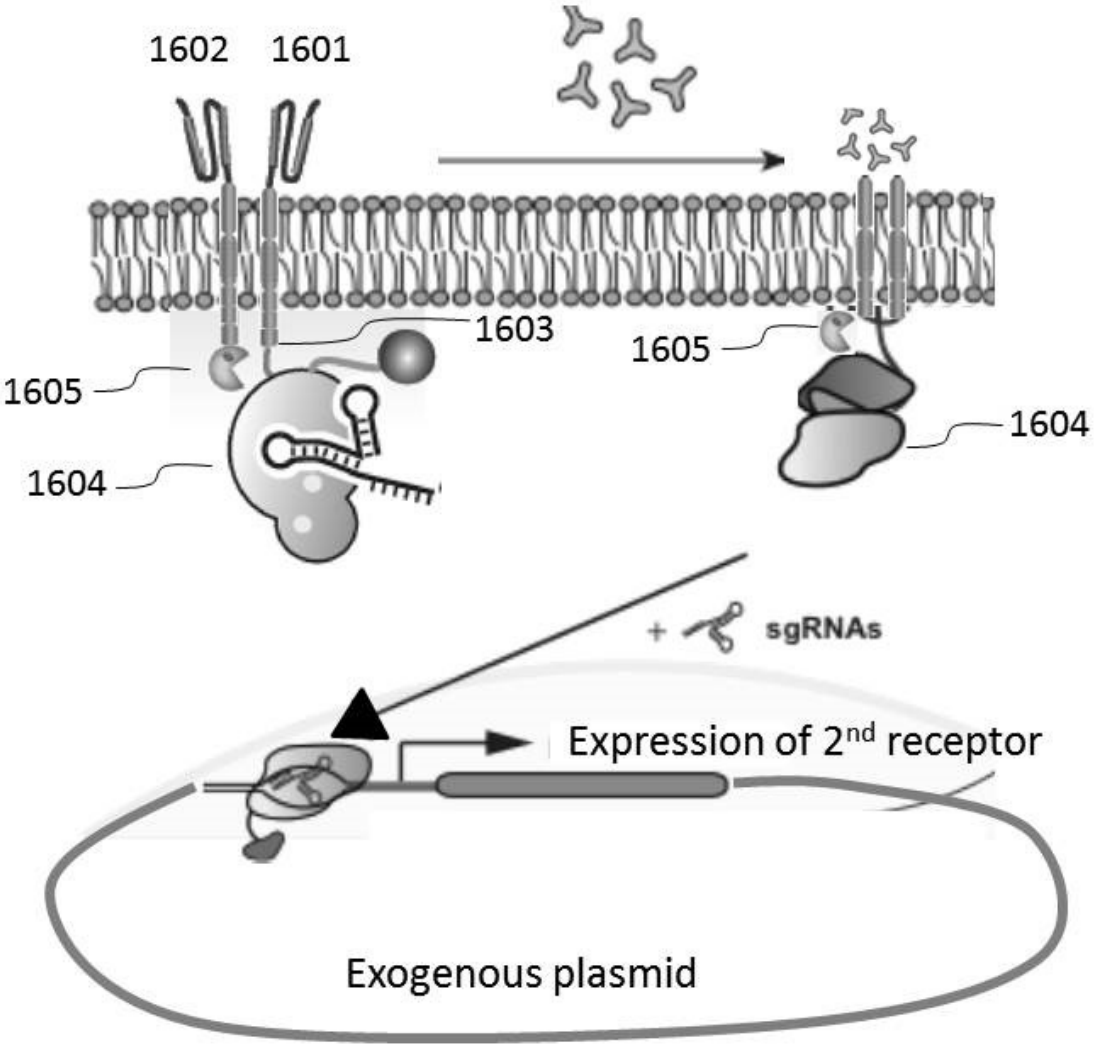

1602
1601
1603
1605
1604
1605
1604
+ sgRNAs
Expression of 2nd receptor
Exogenous plasmid

***FIGURE 16***

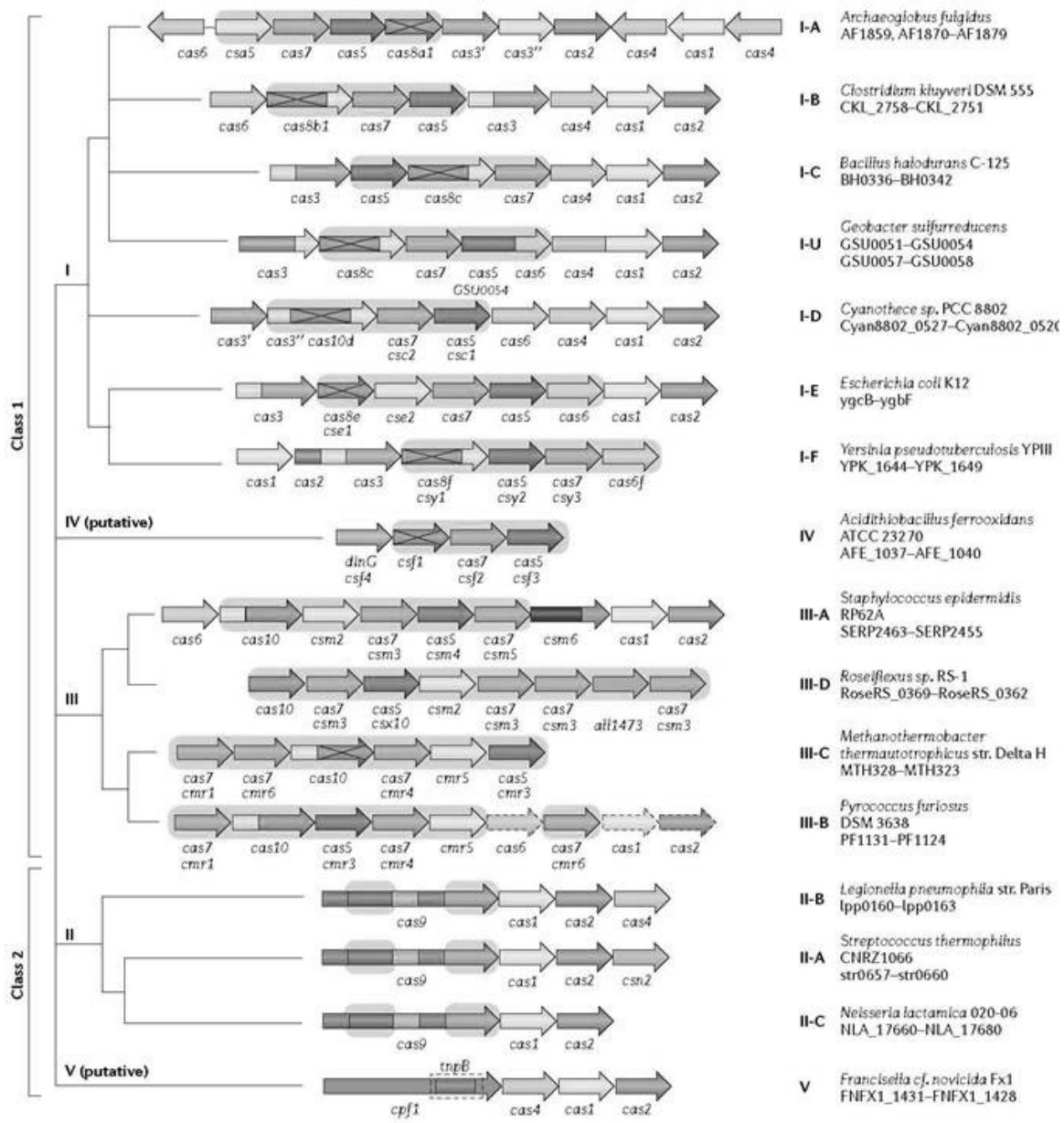

Class 1
Class 2
I
IV (putative)
III
II
V (putative)
cas6 csa5 cas7 cas5 cas8a1 cas3' cas3'' cas2 cas4 cas1 cas4
I-A Archaeoglobus fulgidus AF1859, AF1870–AF1879
cas6 cas8b1 cas7 cas5 cas3 cas4 cas1 cas2
I-B Clostridium kluyveri DSM 555 CKL_2758–CKL_2751
cas3 cas5 cas8c cas7 cas4 cas1 cas2
I-C Bacillus halodurans C-125 BH0336–BH0342
cas3 cas8c cas7 cas5 cas6 cas4 cas1 cas2
GSU0054
I-U Geobacter sulfurreducens GSU0051–GSU0054 GSU0057–GSU0058
cas3' cas3'' cas10d cas7 csc2 cas5 csc1 cas6 cas4 cas1 cas2
I-D Cyanothece sp. PCC 8802 Cyan8802_0527–Cyan8802_052(
cas3 cas8e cse1 cse2 cas7 cas5 cas6 cas1 cas2
I-E Escherichia coli K12 ygcB–ygbF
cas1 cas2 cas3 cas8f csy1 cas5 csy2 cas7 csy3 cas6f
I-F Yersinia pseudotuberculosis YPIII YPK_1644–YPK_1649
dinG csf4 csf1 cas7 csf2 cas5 csf3
IV Acidithiobacillus ferrooxidans ATCC 23270 AFE_1037–AFE_1040
cas6 cas10 csm2 cas7 csm3 cas5 csm4 cas7 csm5 csm6 cas1 cas2
III-A Staphylococcus epidermidis RP62A SERP2463–SERP2455
cas10 cas7 csm3 cas5 csx10 csm2 cas7 csm3 cas7 csm3 all1473 cas7 csm3
III-D Roseiflexus sp. RS-1 RoseRS_0369–RoseRS_0362
cas7 cmr1 cas7 cmr6 cas10 cas7 cmr4 cmr5 cas5 cmr3
III-C Methanothermobacter thermautotrophicus str. Delta H MTH328–MTH323
cas7 cmr1 cas10 cas5 cmr3 cas7 cmr4 cmr5 cas6 cas7 cmr6 cas1 cas2
III-B Pyrococcus furiosus DSM 3638 PF1131–PF1124
cas9 cas1 cas2 cas4
II-B Legionella pneumophila str. Paris lpp0160–lpp0163
cas9 cas1 cas2 csn2
II-A Streptococcus thermophilus CNRZ1066 str0657–str0660
cas9 cas1 cas2
II-C Neisseria lactamica 020-06 NLA_17660–NLA_17680
tnpB cpf1 cas4 cas1 cas2
V Francisella cf. novicida Fx1 FNFX1_1431–FNFX1_1428

***FIGURE 17***

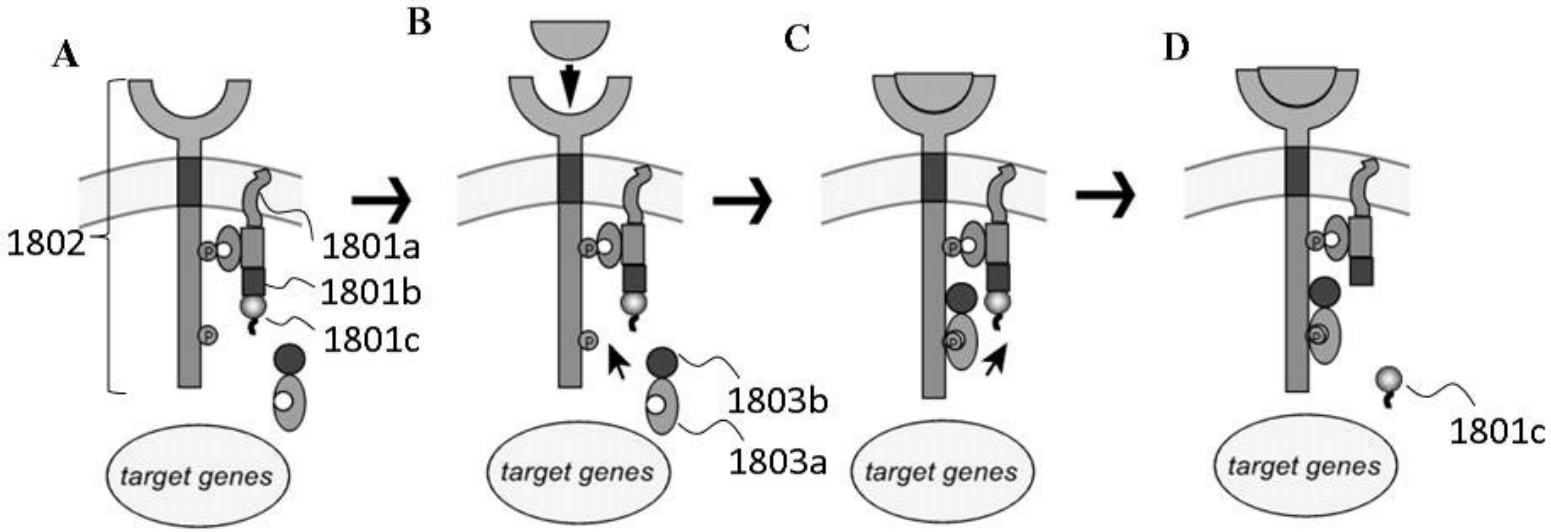

A
B
C
D
1802
1801a
1801b
1801c
1803b
1803a
target genes
target genes
target genes
target genes
1801c

*FIGURE 18*

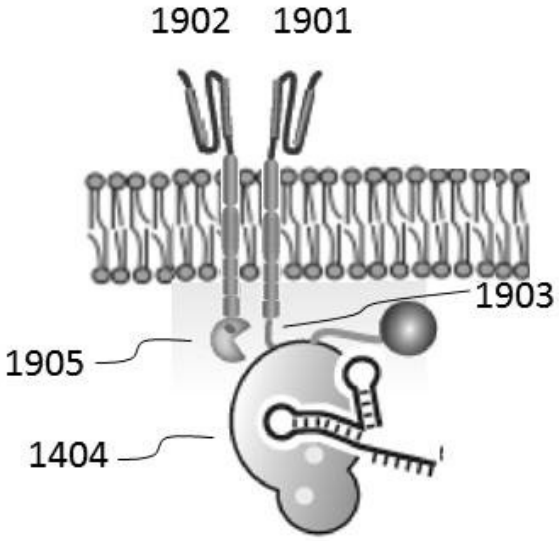
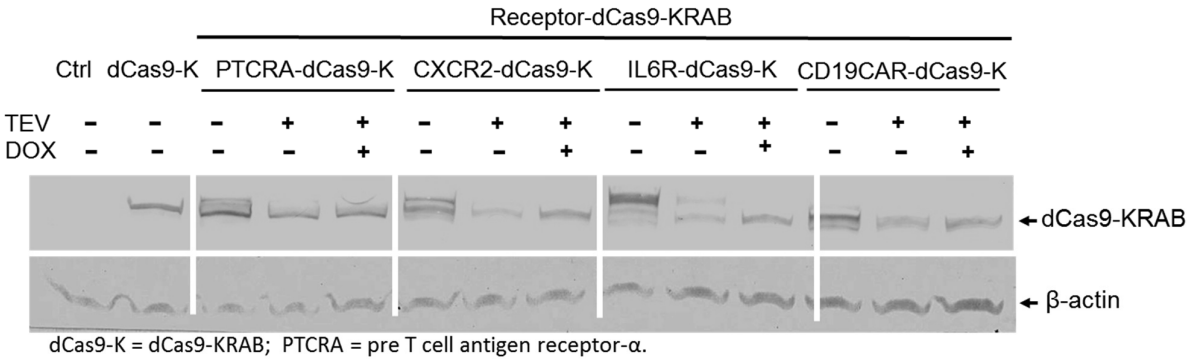



***FIGURE 19***

## *FIGURE 20*




dCas9-K = dCas9-KRAB; PTCRA = pre T cell antigen receptor-α.

## *FIGURE 21*

